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14. ABSTRACT

The objective of this study is to investigate if digital tomosynthesis can fundamentally improve sensitivity of detecting breast masses compared to conventional mammography. Overlapping dense tissue in mammography is one of the most common causes for unnecessary callbacks as well as missed cancers. By removing such overlapping tissue, breast tomosynthesis can obviate unnecessary callbacks as well as missed cancers. The goal is to provide 3D information at high resolution, comparable dose to mammography, and with lower cost and hardware requirements compared to other common alternatives such as breast Computed Tomography (CT) or breast Magnetic Resonance (MR). In the first stage of this study we applied 2-D CAD algorithms to individual projection images of the tomosynthesis data set. We also reconstructed pre-processed projection images using filtered back projection algorithm, where suspicious regions were identified using a DoG filter. Lastly, we studied feasibility of implementing Laguerre-Gauss channelized hotelling observers on mammographic ROIs and compared their performance against that of another visual model proposed by Watson.

15. SUBJECT TERMS
computer aided detection, digital mammography, sub-region hotelling observer, digital tomosynthesis, multi-slice CAD algorithms, biopsy

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INTRODUCTION

For women in the United States, breast cancer is the second-most deadly type of cancer. The American Cancer Society (ACS) estimates that in 2004, breast cancer will be diagnosed in 215,990 women, and will kill an estimated 40,110 women (1). Survival rates are significantly higher when the cancer is detected at an early stage (2-4). At present, the most common, and effective early-detection tool currently available to clinicians is screening mammography, which still misses 10-30% of breast cancers. Two recent developments are designed to aid radiologists in reading mammograms. First, computer-aided detection (CAD) systems for mammography are now commercially available. Mammograms are read more accurately when read by more than one mammographer. Unfortunately, double reading is not practical in the United States. CAD systems have been demonstrated to serve as a reliable, accurate, and efficient second-reader to aid mammographers. One study indicated that a commercial CAD system can successfully identify 77% of overlooked breast malignancies (5), while another demonstrated that routine use of a CAD system may increase the number of cancers detected at screening mammography up to 20% (6). Second, digital tomosynthesis is under active development at this institution and others. These systems provide 3D slice images from a modified digital mammography system.

The purpose of this project is to study the sensitivity of digital tomosynthesis, and investigate its efficacy in detection of breast masses using CAD. It is believed that tomosynthesis will show improvement in characterization, and detection of breast masses by removing overlapping dense fibroglandular tissue. The goal is to provide 3D information at high resolution, comparable dose to mammography, and with lower cost and hardware requirements compared to alternatives such as breast Computed Tomography or breast Magnetic Resonance Imaging.

BODY

Task 1. Translate single-slice CAD algorithms to individual, reconstructed tomosynthesis slice images (Months 1-22):

This task is now under way, with the current emphasis on processing of breast tomosynthesis data from the mentor Dr. Lo's other funded projects. The pace of subject accrual has been steady after February 2006, when the prototype hardware was upgraded and a dedicated clinical coordinator was hired by Dr. Lo. As of now, we have collected a total of 135 cases. Of these approximately 1/3 have lesions that can be used for development of the proposed CAD algorithm.

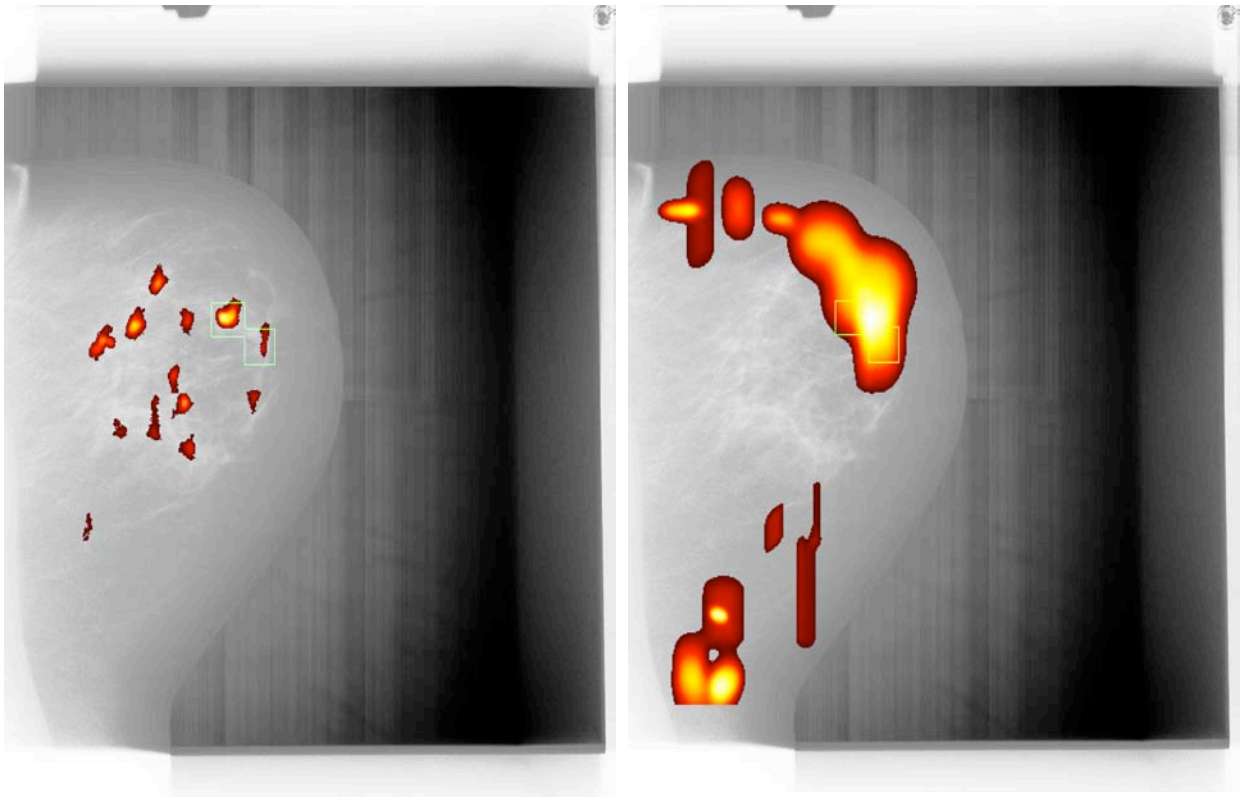
Task 2. Extend CAD algorithms for mass detection interrogating a 3D tomosynthesis volume by studying 3D, multi-slice CAD algorithms for lesion detection and characterization (Months 23-34):

2.1. Apply 2D CAD to projection images prior to 3D tomosynthesis reconstruction (Months 23-28):

We have begun work on task 2.1 well ahead of schedule during this first year, since this work involves the development of basic image processing techniques which can potentially be applied to many of the other aims.

2.1.1 Apply front-end/ high sensitivity/ low-specificity components of 2D CAD to projection images prior to reconstruction.

Since the goal of tomosynthesis is to keep the dose to a patient comparable to that of mammography, each of the 25 projection images obtained for each view is obtained at an extremely low exposure. This results in extremely noisy projection image data. Therefore, for this task, we started with a Difference of Gaussian (DoG) filter to demonstrate feasibility of working with such noisy images. A DoG filter is one of the simpler filters available to us, and the application of this filter was done with the goal of a 'proof of concept.' We also collaborated with our industry partner Siemens and compared our CAD results with that of their commercially available 2-D algorithm. It is to be noted here, that both CAD algorithms were applied "as is" without any re-optimization for these very difficult images, and at this time we are reporting the preliminary results from the initial high sensitivity, low specificity stage.



(a) Duke CAD algorithm *(b) Siemens CAD algorithm*

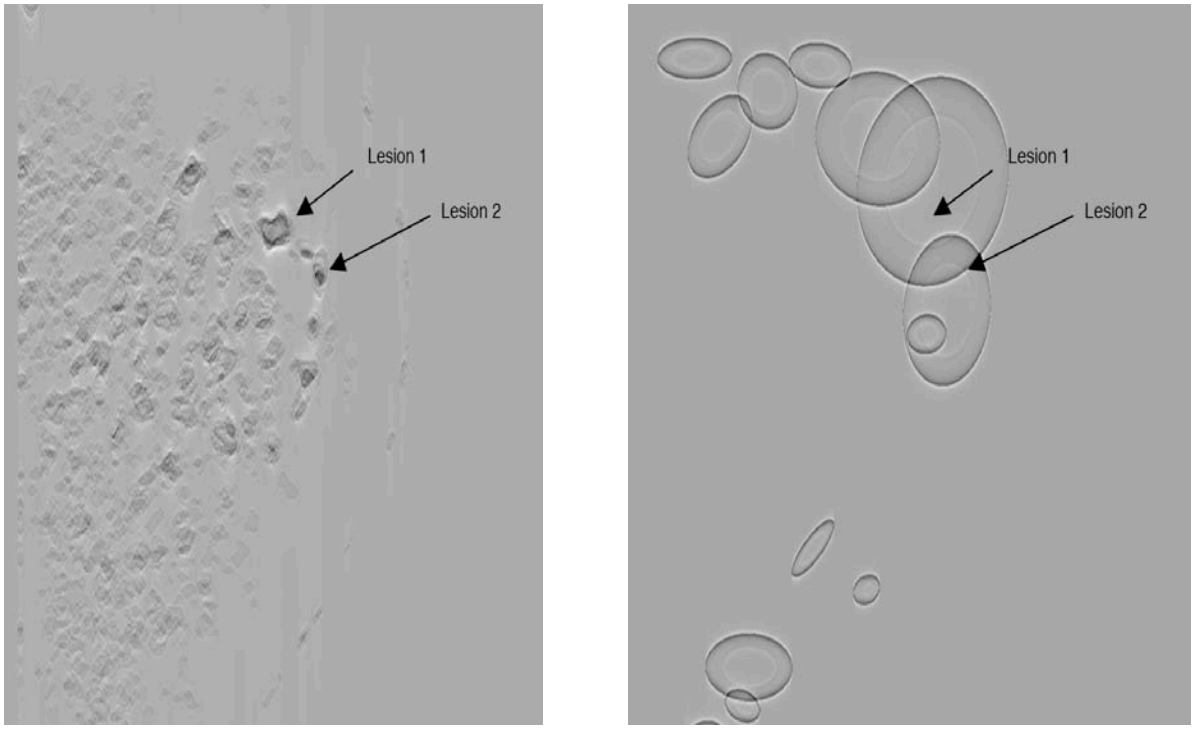
Figure 1: CAD hits projected down to the central projection image from the two algorithms for the subject 33, LMLO view. CAD hits have been shifted and added about the central projection image and are shown in a thermal colormap. The truths are shown using green bounding boxes

The CAD systems from Siemens and Duke performed with 58% and 51.6% sensitivity respectively, while generating 2.3 and 24.9 false positives per breast volume, respectively. It is to be noted that our data set is a difficult data set in which radiologists using mammography performed with only 65% sensitivity. Although the sensitivity and specificity both require considerable further improvement, note again these are

preliminary results before the re-optimization of the algorithms for this type of image and the use of any false positive reduction. These results demonstrate preliminary proof of concept for now, and the very different appearance in CAD detection results from the two algorithms may also allow fusion of the results in the future.

Work for this specific aim resulted in an abstract submission at the Radiological Society of North America conference for 2006 (reportable outcome #1), the largest clinical conference in the field of medical imaging.

2.1.2 Reconstruct pre-processed projection images using filtered backprojection algorithm, where suspicious regions are identified by global thresholding.
Digital Tomosynthesis is an inherently three-dimensional imaging technique that allows reconstruction of an arbitrary set of planes in the breast from limited-angle series of projection images as the x-ray source moves. Filtered Back Projection (FBP) algorithms have traditionally been used in Computed Tomography.



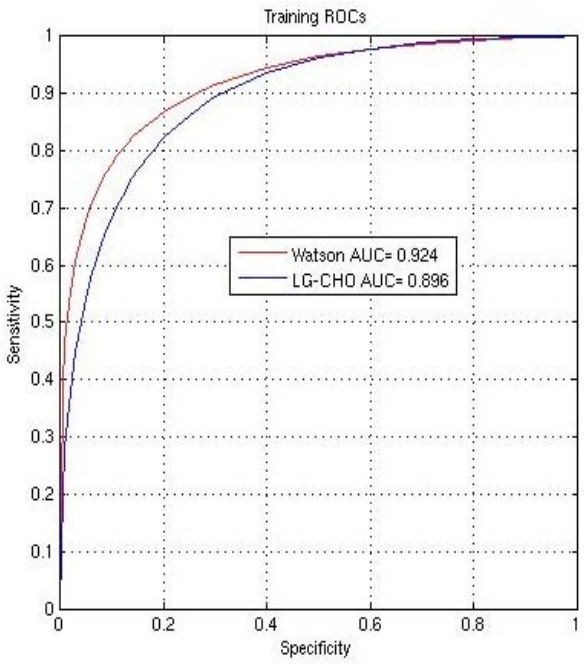
(a) Duke CAD algorithm *(b) Siemens CAD algorithm*
Figure 2: CAD hits when reconstructed using the FBP algorithm from the two algorithms for subject 33, LMLO view.

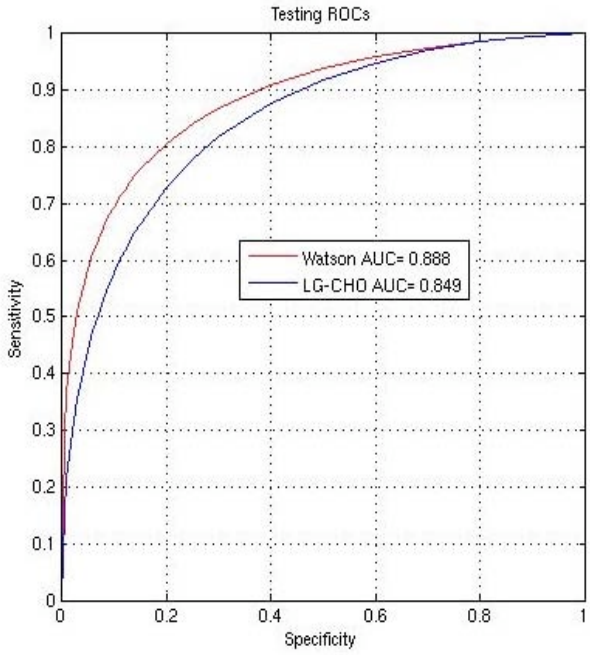
For tomosynthesis reconstruction, based on the central slice theorem, a parallel projection samples the object on a plane perpendicular to the projection plane. The algorithm is: (a) Fourier transform the original projection images into frequency space, (b) Multiply the inverse sampling density filter, (c) Apply hamming window, (d) Shift and add the filtered projection in spatial space for reconstruction (7). We used the FBP

algorithm to reconstruct our CAD hits and two examples of those hits are shown above in figure 2.

2.2. Implement a Laguerre-Gauss Channelized Hotelling Observer (LG-CHO) for 3D mass detection (Months 29-33)

Work on this task also began well ahead of schedule during this first year, again because the results may affect our approach to other aims. Human vision models have been shown to capture the response of the visual system; their incorporation into the classification stage of a CAD system could improve performance. We needed to answer two research questions for this task – (a) how does the performance of LG-CHOs compare against a few other visual models touted as superior models in scientific literature and (b) how does the LG-CHO perform when working with mammograms. It was important to ascertain feasibility of using LG-CHOs with mammograms before proceeding to work with the low dose projection images of the tomosynthesis data set.





(a) Training ROC curves *(b) Testing ROC curves*

Figure 3: The training and testing ROC curves of the two models being compared. (a) The Watson filter bank shows a slightly better training performance compared to the LG-CHO (p=0.13). (b) The Watson filter bank performs significantly better than the LG-CHO and the difference is significant (p=0.029).

To this end, we designed a study that sought to compare the performance of an automated breast mass detection system by using the Watson filter model versus a LG-CHO when working with mammographic data. The LG-CHO and the Watson filter model were trained and tested on a 512x512 ROI database acquired from the Digital Database of Screening Mammography consisting of 800 total ROIs; 200 of which were malignant, 200 were benign and 400 were normal. Half of the ROIs were used to train the weights for ten LG-CHO templates that were later used during the testing stage. For the Watson filter model, the training cases were used to

optimize the frequency filter parameter empirically to yield the best ROC Az performance. This set of filter parameters was then tested on the remaining cases.

The training Az for the LG-CHO and the Watson filter was 0.896 +/- 0.016 and 0.924 +/- 0.014 respectively. The testing Az for the LG-CHO and Watson filter was 0.849 +/- 0.019 and 0.888 +/- 0.017. These results are shown in figure 3 on the previous page. With a p-value of 0.029, the difference in testing performance was statistically significant, thus implying that the Watson filter model holds promise for better detection of masses. This task is a work in progress and initial results show that there might be better visual models that can be used with x-ray data from modalities such as mammograms and tomosynthesis.

Work for this specific task resulted in a proceedings paper at SPIE, the primary scientific conference for medical imaging in 2006 (reportable outcome #2).

Task 3. Evaluate performance of CAD model on independent testing subset of cases (Months 34-36)
Once CAD parameters have been optimized and a functional tool is in place, we will conduct the testing to evaluate performance.

KEY RESEARCH ACCOMPLISHMENTS

- Applied the high sensitivity, low specificity stage of 2D CAD to projection images of the tomosynthesis data and compared performance against other algorithms.
- Reconstructed pre-processed projection images using both Shift and Add and FBP reconstruction algorithms.
- Demonstrated feasibility of working with LG-CHOs for mammograghic ROIs hence showing viability of working with similar visual models for future research with tomosynthesis data.

REPORTABLE OUTCOMES

The following manuscript and abstract are attached at appendices 1 and 2 with the same numbers. The names of the fellow (Singh) and mentor (Lo) are boldfaced for emphasis.

1. **Singh S**, Chaudhuri K, Merlet N, Ratner E, Baker JA, **Lo JY**, “Computer aided detection in breast tomosynthesis: Comparison of preliminary techniques from two institutions,” *RSNA 2006,* (abstract submitted).
2. **Singh S**, Baydush A, Harrawood B, **Lo JY**, “Mass detection in mammographic ROIs using Watson filters,” Medical Imaging 2006: Image Perception, 2006.

CONCLUSIONS

We have demonstrated feasibility of developing a CAD algorithm using observer models with the extremely low-dose tomosynthesis projection slices. Future work will expand the data set size, explore direct optimization of the CAD techniques for tomosynthesis projection images, and perform decision fusion between the CAD algorithms of the two institutions – Duke University and Siemens Medical Solutions, which have very different sensitivity and specificity characteristics to yield better results.

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Appendix

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Computer aided detection in breast tomosynthesis: Comparison of preliminary techniques from two institutions

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PURPOSE

To investigate feasibility of a computer aided detection (CAD) algorithm to locate suspicious breast lesions using breast tomosynthesis clinical data.

METHOD AND MATERIALS

A prototype breast tomosynthesis system by Siemens Medical Solutions was developed to acquire 25 projection images over a 50 degree angular range in approximately 13 seconds. The system uses an amorphous selenium direct digital detector with a large area (23x29 cm), high resolution (85 micron pixel size), and 2 images/second frame rate. One hundred human subjects were recruited, consisting of 65 routine screening, 25 diagnostic mammography, and10 cases undergoing biopsy. Bilateral MLO views was acquired in screening cases, while bilateral MLO and CC views were acquired for diagnostic and biopsy cases. Two existing CAD algorithms for mammography from Siemens and Duke were applied without any further optimization to the low-dose projection images. The projection CAD results were then reconstructed by a shift-and-add technique, yielding a 3D distribution of locations for suspicious lesions within each breast.

RESULTS

The CAD systems from Siemens and Duke performed with 33% and 48% sensitivity, while generating 2.5 and 31 false positives per breast volume, respectively. This was a difficult data set in which radiologists using mammography performed with only 65% sensitivity. Note also that these preliminary algorithms were not optimized for the low exposures of breast tomosynthesis, nor was any false positive reduction scheme used.

CONCLUSION

We demonstrated feasibility for a CAD system for breast tomosynthesis. Future work will expand the data set size, explore direct optimization of the CAD techniques for tomosynthesis projection images, and perform decision fusion between these two institutions' CAD algorithms which have very different sensitivity and specificity characteristics.

CLINICAL RELEVANCE/APPLICATION

This first CAD study based on this manufacturer's unique breast tomosynthesis prototype shows potential for CAD to improve workflow, sensitivity, and specificity.

Mass Detection in Mammographic ROIs Using Watson Filters

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ABSTRACT

Human vision models have been shown to capture the response of the visual system; their incorporation into the classification stage of a Computer Aided Detection system could improve performance. This study seeks to improve the performance of an automated breast mass detection system by using the Watson filter model versus a Laguerre Gauss Channelized Hotelling Observer (LG-CHO). The LG-CHO and the Watson filter model were trained and tested on a 512x512 ROI database acquired from the Digital Database of Screening Mammography consisting of 800 total ROIs; 200 of which were malignant, 200 were benign and 400 were normal. Half of the ROIs were used to train the weights for ten LG-CHO templates that were later used during the testing stage. For the Watson filter model, the training cases were used to optimize the frequency filter parameter empirically to yield the best ROC Az performance. This set of filter parameters was then tested on the remaining cases. The training Az for the LG-CHO and the Watson filter was 0.896 +/- 0.016 and 0.924 +/- 0.014 respectively. The testing Az for the LG-CHO and Watson filter was 0.849 +/- 0.019 and 0.888 +/- 0.017. With a p-value of 0.029, the difference in testing performance was statistically significant, thus implying that the Watson filter model holds promise for better detection of masses.

1. INTRODUCTION

For women in the United States, breast cancer is the second-most deadly type of cancer. The American Cancer Society estimated that in 2004 alone, breast cancer was diagnosed in 215,990 women, and killed an estimated 40,110 women (1). Survival rates are significantly higher when the cancer is detected at an early stage (2-4). The 5-year survival rate (YSR) for patients with localized breast cancer is 97%. Patients with distant metastases see their 5 YSR drop to 23%. Therefore, detecting breast cancer at an early stage is critical to patient care. At present, the most common, and effective early-detection tool currently available to clinicians is screening mammography. In previous work, Laguerre Gauss Channelized Hotelling Observer (LG-CHO) image processing filters have been used to mimic the human visual system with encouraging performance for the automated detection of breast masses in digitized mammograms (8).

In past research, Hotelling observers have been shown to effectively track human observer performance (9-14). The LG-CHO was one of the first human vision based models applied to the task of breast mass detection. In this study we propose to explore a more complex model based on the human visual system that was proposed by Watson (15). Watson's model is based on Gabor functions as first described by Gabor in 1946 (16). As shown by Watson, this human vision based model is a good approximation to the simple cortical cell receptive fields of humans. This study seeks to improve the performance of a Computer Aided Detection (CAD) system for the task of mass detection by using filter response values from the Watson model as features. Performance will be compared against the

previously reported LG-CHO filter. To the best of our knowledge, Watson filters have never been applied to automatic detection tasks in imaging.

2. METHODS AND MATERIALS

2.1 Database

Since this study proposes to test the possibility of using banks Gabor kernels for mass detection, we needed to create a database of Regions of Interest (ROIs). ROIs were extracted from the publicly available Digital Database for Screening Mammography (DDSM) (17) collected by the University of South Florida. Only images from the Lumisys scanner digitized at 50-micron resolution were used. These 512x512 pixel ROIs were obtained with no sub-sampling. A total of 800 such ROIs were collected – 200 of which were malignant, 200 were benign, and 400 were normal ROIs. Of these, 100 malignant, 100 benign, and 200 normal ROIs were randomly assigned to the training group, while the other half of the ROIs were put in testing group.

2.2 Laguerre- Gauss functions

As described by Barrett et al (18), the Laguerre polynomials are defined by:

$$L_n(x) = \sum_{m=0}^{n} (-1)^m \binom{n}{m} \frac{x^m}{m!} \tag{1}$$

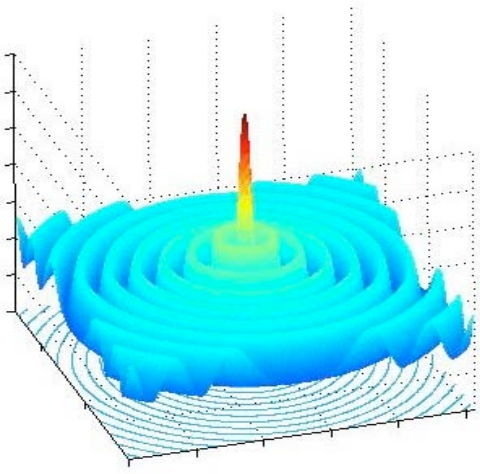
Where the first few polynomials are:

$$L_0(x) = 1 \qquad L_1(x) = -x + 1 \qquad L_2(x) = \frac{1}{2!}\left(x^2 - 4x + 2\right) \tag{2}$$

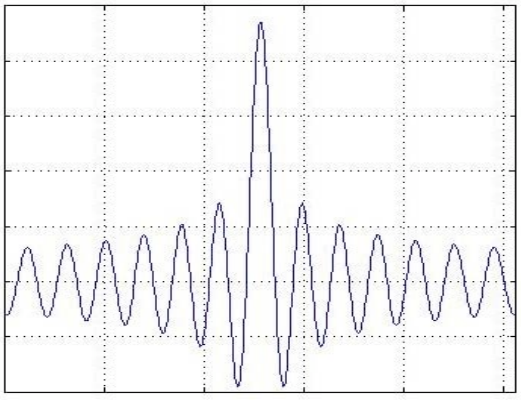
The Laguerre polynomials are orthonormal on (0, ∞) with respect to an exponential weight factor and the change of variables $x = \frac{2\pi r^2}{a^2}$ yields a new orthonormal family. Barrett et al give a possible expansion in continuous polar coordinates with origin at the signal location for the template as:

$$w(r,\theta) = \sum_n \sum_m \alpha_{nm} \exp\left(\frac{-\pi r^2}{a^2}\right) L_n\left(\frac{2\pi r^2}{a^2}\right) e^{im\theta} \tag{3}$$

A sample 25 channel LG-CHO template is shown in figure 1 below.



(a)



(b)

Figure 1: ***(a)*** *3-D representation of a 25 channel LG-CHO* ***(b)*** *2-D representation of the 25 channel LG-CHO by taking a profile through the mid-plane of (a)*

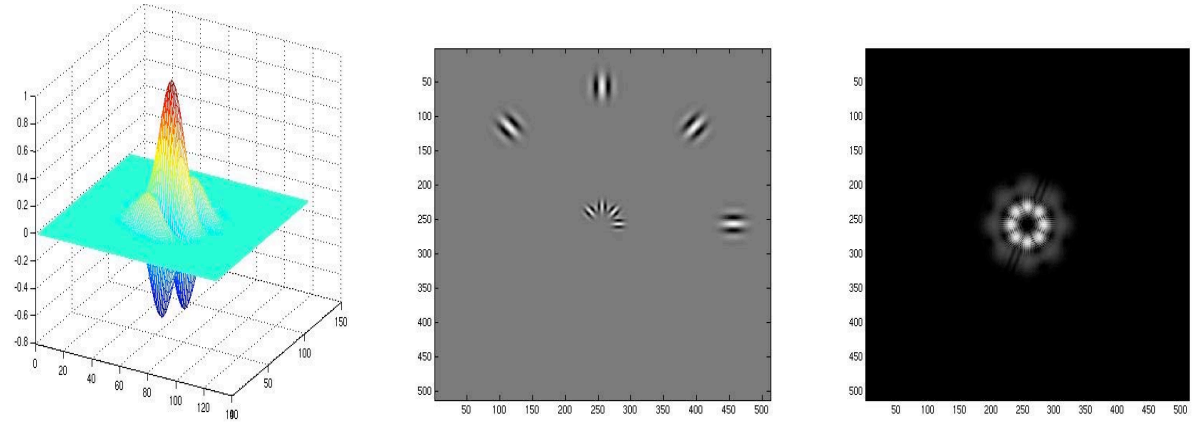
For further reading on channelized hotelling observers, readers are referred to some of the excellent references in this subject, (18-22).

2.3 Gabor Kernels

Gabor kernels measure the change on an image in a certain direction or on a certain scale, thereby describing a texture with respect to direction and size and strength (23). As defined by Watson, each Gabor kernel is given by the equation:

$$w(x,y) = \exp^{-4*\ln 2*(x^2+y^2/w^2} * \cos[(2\pi f(x\cos\theta + y\sin\theta) + \phi] \quad (4)$$

Where f is the spatial frequency, θ is the orientation, w is the width, and ϕ is the phase. The frequency and width were related by using the relation $f = \frac{3}{2} * \frac{4\ln 2}{\pi w}$.



(a) (b) (c)

Figure 2: ***(a)*** *3-D representation of a single Gabor kernel in the spatial domain* ***(b)*** *2-D spatial domain representation of a filter bank of Gabor kernels with 4 kernels placed at every 45° from -45° to +90° at a radius of 25 and 200 pixels from the center of the image. The frequency for the inner radius is 0.8727 cycles/ degree and that of the outer radius is 0.4363 cycles/ degree* ***(c)*** *Frequency domain representation of (b)*

2.4 Experimental Design

LG-CHO: To obtain the LG-CHO performance, optimized parameter values of the number of channels and order were used as described by Baydush et al (8). The 400 training ROIs were used to obtain channel weights for each of the templates for the 25 channels. The weights and templates thus obtained were then used in testing of the other 400 ROIs.

Watson Filter Bank: Although some analytical work has been done to demonstrate the efficacy of certain similar types of filters as used in the Watson model, the relationships between texture differences and the filter configurations required to discriminate them remain largely unknown.

For our study we chose to keep a fixed radial distance of each of the Gabor kernels at 25, 100, and 150 pixels from the center of the ROI. This corresponds to a distance of 1, 5, and 7 mm respectively. These radii were chosen based on the average mass size, which is typically about 5 mm in diameter. Thus, these radii allow us to place a set of Gabor kernels inside the average mass, a second set of kernels right at the margin of an average mass, and lastly a set of kernels just outside the mass margins of an average mass. We chose a radial sampling angle of 45^0 to keep the complexity of the filter bank within a manageable range. Therefore, each filter bank had 24 Gabor kernels arranged in three concentric circles of pairs of eight kernels. The frequency parameter was varied over a range of values and the individual performance on the training set was evaluated. The frequency was varied over a range of 0.0105 to 0.3142 cycles/ degree in increments of 0.0052 cycles/ degree. This variation of the frequency parameter resulted in a total of 59 filter banks each consisting of 24 kernels. The performances and the response of the ROIs to each of these were evaluated and compared. Performance was measured in terms of receiver operating characteristic (ROC) area index Az, which was calculated and compared using LABROC4 and CLABROC software (Charles Metz, University of Chicago). The best performing template was chosen and used along with the training weights on the testing cases to determine testing performance.

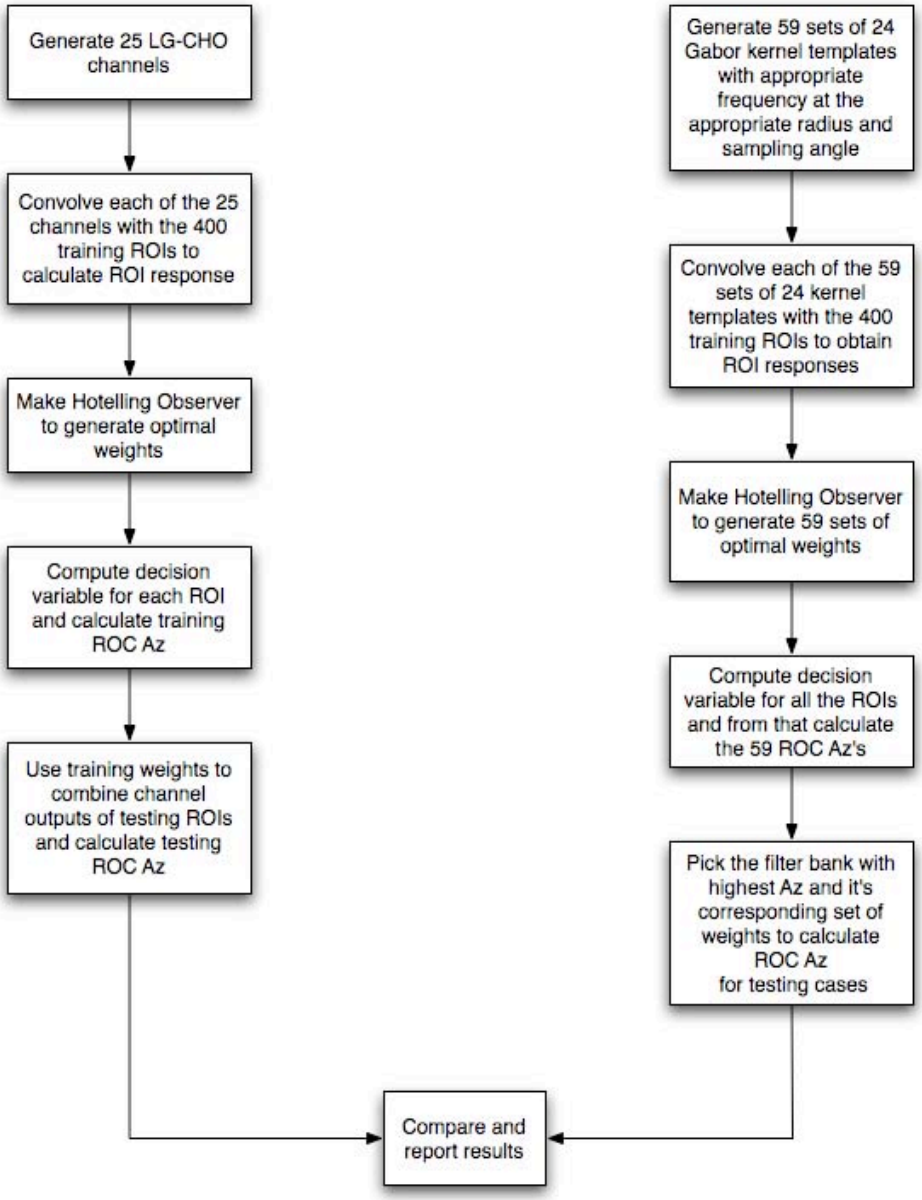


Figure 3: Flowchart demonstrating experimental design

3. RESULTS

Training and testing ROC curves for the LG-CHO and the best performing Watson filter bank were computed. The training Az for the LG-CHO and the Watson filter was 0.896 +/- 0.016 and 0.924 +/- 0.014 respectively. The testing Az for the LG-CHO and Watson filter was 0.849 +/- 0.019 and 0.888 +/- 0.017. There was no significant difference in the training Az performance between the two models (p=0.13). The two-tailed p-value for testing was 0.029. This was a significant difference, thus implying that the Watson filter bank holds promise for better detection of masses.

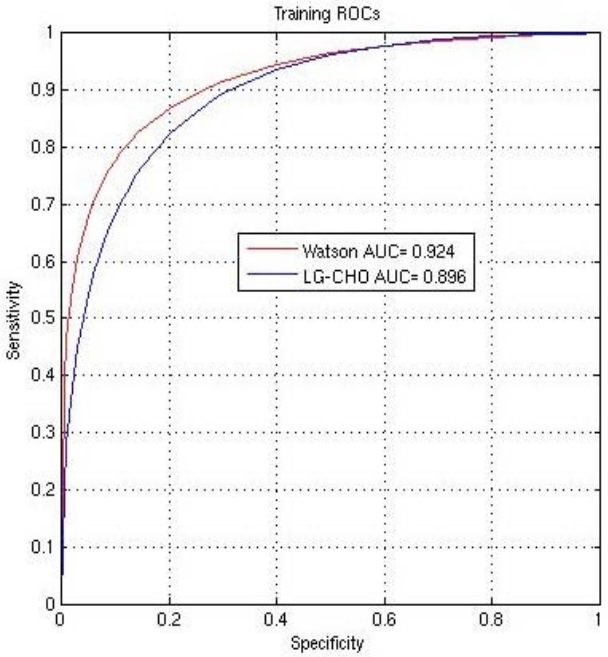


Figure 4: The training ROC curves of the two models being compared. The Watson filter bank shows a slightly better training performance compared to the LG-CHO (p=0.13).

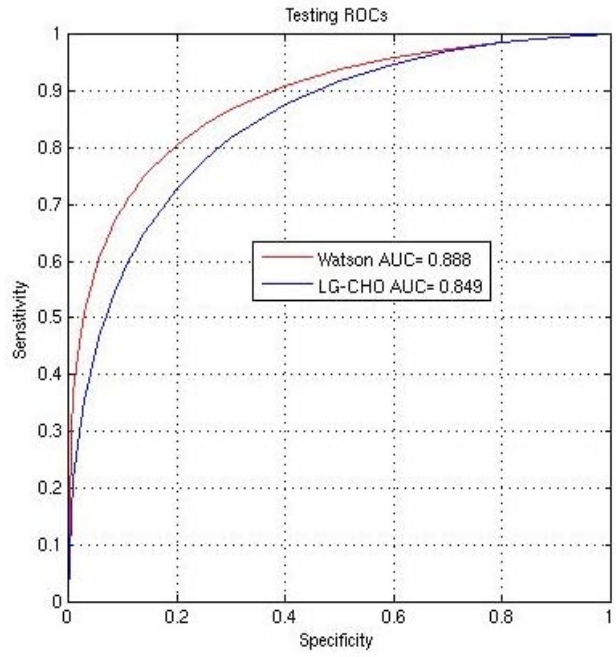


Figure 5: The testing ROC curves of the two models being compared. The Watson filter bank performs significantly better than the LG-CHO and the difference is significant (p=0.029).

It should be noted that the LG-CHO and Watson filter bank have comparable levels of complexity as far as the number of templates is concerned. The LG-CHO model has 25 templates, while the Watson model has 24 templates. In each of the two filters, a Hotelling Observer was used to assign weights to the templates. The testing results for the Watson filter bank model shows that it is able to generalize well to new cases, and does not significantly overtrain during the training of the weights by the Hotelling Observer.

These results are encouraging enough to warrant further study. For our study we had fixed a number of parameters in order to reduce the multi-dimensional parameter search space. Further work needs to be done to explore the effect of the fixed parameters such as number of concentric rings, the radii of these rings from the center of the ROI, and the radial sampling. The parameter space for frequency needs to be widened as well. Furthermore, experiments to study the role of the Watson filter bank for diagnosis are called for as well.

4. CONCLUSIONS

The Watson filter bank model was able to out-perform the LG-CHO model. These results suggest that there is potential for better performance with the Watson filter bank model with relatively low risk of overtraining. Further study is definitely warranted, including the use of larger data sets, more rigorous optimization of the Watson filter bank model parameters, and application to full images instead of ROIs.

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